Supplementary Material*

Mehrotra DV, Janes HE, Fleming TR, et al. Clinical endpoints for evaluating efficacy in COVID-19 vaccine trials. Ann Intern Med. 22 October 2020. [Epub ahead of print]. doi:10.7326/M20-6169

Supplement Table 1. Summary Statistics and Plug-In Vaccine Efficacy Estimators

Treatment Arm (Number Randomized)	Number Uninfected	Number Infected			Mean burden of disease (BOD) score [Y] among COVID cases (i.e., for those with Y>0)
		Asymptomatic (No COVID)	Symptomatic Nonsevere COVID	Symptomatic Severe COVID	
	BOD=0	BOD=0	BOD=1	BOD=2	
Placebo (N_p)	a_p	b_p	c_p	d_p	$\bar{y}_p = 1 + \frac{d_p}{c_p+d_p}$
Vaccine ($N_v = kN_p$)	a_v	b_v	c_v	d_v	$\bar{y}_v = 1 + \frac{d_v}{c_v+d_v}$
$N = N_p + N_v$	$a = a_p + a_v$	$b = b_p + b_v$	$c = c_p + c_v$	$d = d_p + d_v$	$\leftarrow$ Totals

In this report, *infection* means SARS-CoV-2 infection and *disease* means COVID-19 disease, the latter also referred to as COVID. With reference to the table above, in treatment arm i (with $i=v$ for vaccine and $i=p$ for placebo), we let $m_i = b_i + c_i + d_i$ and $n_i = c_i + d_i$ denote the number of participants diagnosed with SARS-CoV-2 infection and the number of participants diagnosed with COVID-19 disease, respectively. Due to the anticipated low incidence rate for each binary endpoint, it is reasonable to assume that the case counts in the vaccine and placebo arms follow Poisson distributions with parameters generically labeled λ_v and λ_p, respectively. Vaccine efficacy (VE) is defined as $1 - RR$, where $RR=\lambda_v/\lambda_p$ is the relative risk. Conditional on the total number of cases (vaccine and placebo arms combined), the number of cases in the vaccine arm follows a binomial distribution with parameter $RR/[RR+(1/k)]$, where $k=N_v/N_p$ is the randomization ratio. This conditional binomial distribution is used below to illustrate how vaccine efficacy can be easily estimated using case counts for a given binary endpoint. (Other more sophisticated statistical approaches can also be considered, including time-to-event methods not discussed in this report.)

Infection (I)
$$\widehat{RR}_I = \frac{1}{k}\frac{m_v}{m_p}, \quad \widehat{VE}_I = 1 - \widehat{RR}_I$$

Asymptomatic Infection (AI)
$$\widehat{RR}_{AI} = \widehat{RR}_I\widehat{RR}_{AI|I} = \left(\frac{1}{k}\frac{m_v}{m_p}\right)\left(\frac{b_v/m_v}{b_p/m_p}\right) = \frac{1}{k}\frac{b_v}{b_p}, \quad \widehat{VE}_{AI} = 1 - \widehat{RR}_{AI}$$

COVID (D)
$$\widehat{RR}_D = \widehat{RR}_I\widehat{RR}_{D|I} = \left(\frac{1}{k}\frac{m_v}{m_p}\right)\left(\frac{n_v/m_v}{n_p/m_p}\right) = \frac{1}{k}\frac{n_v}{n_p}, \quad \widehat{VE}_D = 1 - \widehat{RR}_D$$

Nonsevere COVID (NS)
$$\widehat{RR}_{NS} = \widehat{RR}_I\widehat{RR}_{D|I}\widehat{RR}_{NS|D} = \left(\frac{1}{k}\frac{m_v}{m_p}\right)\left(\frac{n_v/m_v}{n_p/m_p}\right)\left(\frac{c_v/n_v}{c_p/n_p}\right) = \frac{1}{k}\frac{c_v}{c_p}, \quad \widehat{VE}_{NS} = 1 - \widehat{RR}_{NS}$$

Severe COVID (S)
$$\widehat{RR}_S = \widehat{RR}_I\widehat{RR}_{D|I}\widehat{RR}_{S|D} = \left(\frac{1}{k}\frac{m_v}{m_p}\right)\left(\frac{n_v/m_v}{n_p/m_p}\right)\left(\frac{d_v/n_v}{d_p/n_p}\right) = \frac{1}{k}\frac{d_v}{d_p}, \quad \widehat{VE}_S = 1 - \widehat{RR}_S$$

Burden of Disease (BOD)
$$\widehat{RR}_{BOD} = \widehat{RR}_I\widehat{RR}_{D|I}\frac{\hat{E}(Y|Y>0, v)}{\hat{E}(Y|Y>0, p)} = \left(\frac{1}{k}\frac{m_v}{m_p}\right)\left(\frac{n_v/m_v}{n_p/m_p}\right)\left(\frac{\bar{y}_v}{\bar{y}_p}\right) = \frac{1}{k}\frac{n_v}{n_p}\frac{\bar{y}_v}{\bar{y}_p}, \quad \widehat{VE}_{BOD} = 1 - \widehat{RR}_{BOD}$$

Note that $\widehat{RR}_{BOD} = \widehat{RR}_D\left(\frac{1+\frac{d_v}{n_v}}{1+\frac{d_p}{n_p}}\right)$

Analysis of Disease Endpoint (COVID-19)

Analysis conditions on the total number of disease cases (n)

- $H_{D,null}: VE_D \leq VE_{D,null}$ vs. $H_{D,alt}: VE_D > VE_{D,null}$

- $RR_{D,null} = 1 - VE_{D,null}, RR_D = 1 - VE_D$

- $n_v|n \sim Binomial(n, \pi_v = kRR_D/[1 + kRR_D]), n = n_v + n_p$

- Analysis option 1 (exact method)

  $\pi_{v,UB[exact]} = \text{BETAINV}(1 - \alpha, n_v + 1, n - n_v)$

  Lower bound (LB) of exact 100x(1-2α)% CI for VE_D is: $VE_{D,LB[exact]} = 1 - \frac{\pi_{v,UB[exact]}}{k(1 - \pi_{v,UB[exact]})}$

  $\pi_{v,LB[exact]} = \text{BETAINV}(\alpha, n_v, n - n_v + 1)$

  Upper bound (UB) of exact 100x(1-2α)% CI for VE_D is: $VE_{D,UB[exact]} = 1 - \frac{\pi_{v,LB[exact]}}{k(1 - \pi_{v,LB[exact]})}$

  Above, BETAINV is a function in SAS and Excel software that calculates required quantiles from a given Beta distribution; it is equivalent to the qbeta function in R software.

- Analysis option 2 (asymptotic method)

  $\widehat{RR}_D = \frac{1}{k}\frac{\hat{\pi}_v}{\hat{\pi}_p}, \widehat{VE}_D = 1 - \widehat{RR}_D$, where $\hat{\pi}_j = \frac{n_j}{n}$ $(j = v, p)$

  $Z_D = \frac{[ln(\widehat{RR}_D) + cc] - ln(RR_{D,null})}{\sqrt{\frac{1}{n}\left(\frac{(1-\hat{\pi}_v)}{\hat{\pi}_v} + \frac{(1-\hat{\pi}_p)}{\hat{\pi}_p} + 2\right)}} \sim$ N(0,1) if $VE_D = VE_{D,null}, cc = ln\left(1 + \frac{1}{n}\right) \cong 0$ for large n

  Lower bound (LB) of asymptotic 100x(1-2α)% CI for VE_D is:

  $$VE_{D,LB[asymptotic]} = 1 - exp\left(ln(\widehat{RR}_D) + cc + Z_{1-\alpha}\sqrt{\frac{1}{n}\left(\frac{(1-\hat{\pi}_v)}{\hat{\pi}_v} + \frac{(1-\hat{\pi}_p)}{\hat{\pi}_p} + 2\right)}\right)$$

  Upper bound (UB) of asymptotic 100x(1-2α)% CI for VE_D is:

  $$VE_{D,UB[asymptotic]} = 1 - exp\left(ln(\widehat{RR}_D) + cc - Z_{1-\alpha}\sqrt{\frac{1}{n}\left(\frac{(1-\hat{\pi}_v)}{\hat{\pi}_v} + \frac{(1-\hat{\pi}_p)}{\hat{\pi}_p} + 2\right)}\right)$$

The two analysis options above deliver identical inference almost always in moderate to large samples. Note that the denominator of Z_D results from a straightforward derivation using well-known formulas for expectations and variances of ratios and products of potentially correlated random variables and first-order Taylor series approximations. All the theoretically derived formulas and type I error control have been thoroughly validated using extensive simulations (details omitted).

Analysis of Burden of Disease Endpoint (BOD)

Analysis conditions on the total number of disease cases (n)

- $H_{BOD,null}: VE_{BOD} \leq VE_{BOD,null}$ vs. $H_{BOD,alt}: VE_{BOD} > VE_{BOD,null}$

- $RR_{BOD,null} = 1 - VE_{BOD,null}, RR_{BOD} = 1 - VE_{BOD}$

- $n_v|n \sim Binomial(n, \pi_v = kRR_D/[1 + kRR_D]),), n = n_v + n_p$

- $\hat{\pi}_j = \frac{n_j}{n} \ (j = v, p)$

- $\bar{y}_j = 1 + \frac{d_j}{n_j}$ and $s_j^2 = \frac{d_j(n_j - d_j)}{n_j^2}$ are mean and variance of BOD scores among disease cases $(j = v, p)$

- $RR_{BOD} = \frac{1}{k} \frac{\pi_v}{\pi_p} \frac{E(Y|Y>0, v)}{E(Y|Y>0, p)}, \ \widehat{RR}_{BOD} = \frac{1}{k} \frac{n_v}{n_p} \frac{\bar{y}_v}{\bar{y}_p}, \ cc = ln\left(1 + \frac{1}{n}\right) \cong 0$ for large n

- $Z_{BOD} = \frac{[ln(\widehat{RR}_{BOD}) + cc] - ln(RR_{BOD,null})}{\sqrt{\frac{1}{n}\left(\frac{\hat{\pi}_v[s_v^2 + (1-\hat{\pi}_v)\bar{y}_v^2]}{(\hat{\pi}_v\bar{y}_v)^2} + \frac{\hat{\pi}_p[s_p^2 + (1-\hat{\pi}_p)\bar{y}_p^2]}{(\hat{\pi}_p\bar{y}_p)^2} + 2\right)}} \sim N(0,1)$ if $VE_{BOD} = VE_{BOD,null}$

- Lower bound (LB) of asymptotic 100x(1-2α)% CI for VE_{BOD} is:

$$VE_{BOD,LB} = 1 - exp\left(ln(\widehat{RR}_{BOD}) + cc + Z_{1-\alpha}\sqrt{\frac{1}{n}\left(\frac{\hat{\pi}_v[s_v^2 + (1-\hat{\pi}_v)\bar{y}_v^2]}{(\hat{\pi}_v\bar{y}_v)^2} + \frac{\hat{\pi}_p[s_p^2 + (1-\hat{\pi}_p)\bar{y}_p^2]}{(\hat{\pi}_p\bar{y}_p)^2} + 2\right)}\right)$$

- Upper bound (UB) of asymptotic 100x(1-2α)% CI for VE_{BOD} is:

$$VE_{BOD,UB} = 1 - exp\left(ln(\widehat{RR}_{BOD}) + cc - Z_{1-\alpha}\sqrt{\frac{1}{n}\left(\frac{\hat{\pi}_v[s_v^2 + (1-\hat{\pi}_v)\bar{y}_v^2]}{(\hat{\pi}_v\bar{y}_v)^2} + \frac{\hat{\pi}_p[s_p^2 + (1-\hat{\pi}_p)\bar{y}_p^2]}{(\hat{\pi}_p\bar{y}_p)^2} + 2\right)}\right)$$

If nonsevere and severe disease cases are assigned the same score, $Z_{BOD} = Z_D$. Note that the denominator of Z_{BOD} results from a straightforward derivation using well-known formulas for expectations and variances of ratios and products of potentially correlated random variables and first-order Taylor series approximations. All the theoretically derived formulas and type I error control have been thoroughly validated using extensive simulations (details omitted).

Multiplicity Control if Disease and BOD are Dual Primary Endpoints

- Z_D and Z_{BOD} are expected to be highly correlated (~ 0.95)

- $Z_* = \min(Z_D, Z_{BOD})$ {note that more negative Z_* values provide stronger evidence of vaccine efficacy}

- Distribution: $f(z_*) = 2\phi(z_*)\Phi\left(-\dfrac{1-\rho}{\sqrt{1-\rho^2}}z_*\right)$, $\rho = \text{corr}(Z_D, Z_{BOD})$; $\phi(.)$ and $\Phi(.)$ are the density function and cumulative distribution function of the standard normal distribution, respectively.

- $\hat{\rho} = \dfrac{\sqrt{\dfrac{1}{n}\left(\dfrac{(1-\hat{\pi}_v)}{\hat{\pi}_v}+\dfrac{(1-\hat{\pi}_p)}{\hat{\pi}_p}+2\right)}}{\sqrt{\dfrac{1}{n}\left(\dfrac{\hat{\pi}_v[s_v^2+(1-\hat{\pi}_v)\bar{y}_v^2]}{(\hat{\pi}_v\bar{y}_v)^2}+\dfrac{\hat{\pi}_p[s_p^2+(1-\hat{\pi}_p)\bar{y}_p^2]}{(\hat{\pi}_p\bar{y}_p)^2}+2\right)}}$

  One million simulated trials under each of a broad range of scenarios confirm that $\hat{\rho}$ is a very accurate and precise estimator of ρ, and that the negligible variability around $\hat{\rho}$ can be ignored for valid statistical inference.

- With only a single primary endpoint (either D [≡ COVID] or BOD), the FDA success criterion requires that the lower bound (LB) of the 95% confidence interval (CI) for vaccine efficacy (VE) for that endpoint be greater than 30% and the point estimate of VE be at least 50%. In that case, the CI for VE is calculated using the 2.5th percentile of the standard normal distribution (implying the use of $Z_{1-\alpha}$=1.96 in the CI formulas on pages 4-5). However, with dual primary endpoints, the 2.5th percentile of the distribution of Z_* (with $\hat{\rho}$ replacing ρ) is used to calculate a multiplicity-adjusted 95% CI for each of VE_D and VE_{BOD}. Statistical success for a given endpoint is achieved if the lower bound of the multiplicity-adjusted CI is greater than 30% and the point estimate of VE is at least 50%. Statistical power for the scenario with dual primary endpoints (next page) is defined as the probability of correctly achieving a statistical win for at least one of the endpoints.

Supplement Table 2. Statistical Power With Single or Dual Primary Efficacy Endpoints

Simulated design with V:P=2:1, n=147 COVID cases (fixed), α=2.50% (1-tailed)

Assumed Vaccine Efficacy (%)		Determined Vaccine Efficacy (%)*	Statistical power (%) with single or dual primary efficacy endpoint(s)			
COVID	Severe COVID	Nonsevere COVID	Severe COVID	COVID	BOD	COVID, BOD
55	0	69	0	74	29	74
55	30	61	2	74	50	74
55	60	54	26	74	75	77
55	70	51	47	74	82	80
55	80	49	73	74	87	85
55	90	46	94	74	92	90
60	0	75	0	91	47	91
60	30	68	2	91	70	91
60	60	60	27	91	89	92
60	70	57	50	91	93	93
60	80	55	76	91	96	95
60	90	52	95	91	98	97

* Assuming 20% of COVID cases in the placebo arm will be severe (21), VE(COVID) = 0.2xVE(severe COVID) + 0.8xVE(nonsevere COVID), where VE denotes vaccine efficacy. Hence if the first two vaccine efficacy values in this equation are fixed, the third one is determined after invoking the aforementioned assumption. Power for a given efficacy endpoint is based on statistical success defined as a vaccine efficacy point estimate of at least 50% with lower bound of the corresponding 95% confidence interval greater than 30% (5). COVID endpoint scoring is 0=no COVID, 1=COVID and burden of disease (BOD) endpoint scoring is 0=no COVID, 1=nonsevere COVID, 2=severe COVID. Vaccine efficacy is the relative reduction (vs. placebo) in the mean endpoint score, which is equivalent to a relative reduction in incidence for the COVID endpoint. Multiplicity adjustment used for the dual primary endpoint strategy leverages the very high correlation between the COVID and BOD endpoint test statistics (as described on the previous page). Power calculations were done using 1 million simulated trials for each scenario.

Using Hypothetical Data Example to Illustrate Calculation Details

Treatment Arm (Number Randomized)	Number Uninfected	Number Infected			Mean burden of disease (BOD) score among COVID cases
		Asymptomatic (No COVID)	Symptomatic Nonsevere COVID	Symptomatic Severe COVID	
	BOD=0	BOD=0	BOD=1	BOD=2	
Placebo ($N_p = 10{,}000$)	a_p=9,879	b_p=45	c_p=57	d_p=19	$\bar{y}_p = 1 + \frac{19}{57+19}$
Vaccine ($N_v = 20{,}000$)	a_v=19,801	b_v=128	c_v=63	d_v=8	$\bar{y}_v = 1 + \frac{8}{63+8}$
$N = 30{,}000$	$a = 29{,}680$	$b = 173$	$c = 120$	$d = 27$	← Totals

Randomization ratio $= k = 20{,}000/10{,}000 = 2$

Number of infection cases in placebo arm $= m_p = b_p + c_p + d_p = 45 + 57 + 19 = 121$

Number of infection cases in vaccine arm $= m_v = b_v + c_v + d_v = 128 + 63 + 8 = 199$

Total number of infection cases $= m = m_p + m_v = 121 + 199 = 320$

Number of COVID cases in placebo arm $= n_p = c_p + d_p = 57 + 19 = 76$

Number of COVID cases in vaccine arm $= n_v = c_v + d_v = 63 + 8 = 71$

Total number of COVID cases $= n = n_p + n_v = 76 + 71 = 147$

Infection Endpoint

Vaccine efficacy estimate $= 1 - \frac{1}{k}\frac{m_v}{m_p} = 1 - \frac{1}{2}\left(\frac{199}{121}\right) = 17.8\%$

Calculation of exact confidence interval (shown in Figure 2)

$\text{BETAINV}(1 - \alpha, m_v + 1, m - m_v) = \text{BETAINV}(1 - 0.025, 199 + 1, 320 - 199) = 0.67522$

$\text{BETAINV}(\alpha, m_v, m - m_v + 1) = \text{BETAINV}(0.025, 199, 320 - 199 + 1) = 0.56625$

Lower bound of exact 95% CI for vaccine efficacy $= 1 - \frac{0.67522}{2(1-0.67522)} = -4.0\%$

Upper bound of exact 95% CI for vaccine efficacy $= 1 - \frac{0.56625}{2(1-0.56625)} = 34.7\%$

Calculation of asymptotic confidence interval (shown here for completeness)

$\frac{m_p}{m} = \frac{121}{320} = 0.37813, \frac{m_v}{m} = \frac{199}{320} = 0.62188, \ln\left(1 + \frac{1}{m}\right) = \ln\left(1 + \frac{1}{320}\right) = 0.00312$

Lower bound of asymptotic 95% CI for vaccine efficacy

$$= 1 - exp\left(\ln\left(\frac{1}{2}\left(\frac{199}{121}\right)\right) + 0.00312 + 1.96\sqrt{\frac{1}{320}\left(\frac{(1 - 0.62188)}{0.62188} + \frac{(1 - 0.37813)}{0.37813} + 2\right)}\right) = -3.4\%$$

Upper bound of asymptotic 95% CI for vaccine efficacy

$$= 1 - exp\left(\ln\left(\frac{1}{2}\left(\frac{199}{121}\right)\right) + 0.00312 - 1.96\sqrt{\frac{1}{320}\left(\frac{(1 - 0.62188)}{0.62188} + \frac{(1 - 0.37813)}{0.37813} + 2\right)}\right) = 34.2\%$$

Asymptomatic Infection Endpoint

Vaccine efficacy estimate $= 1 - \frac{1}{k}\frac{b_v}{b_p} = 1 - \frac{1}{2}\left(\frac{128}{45}\right) = -42.2\%$

Calculation of exact confidence interval (shown in Figure 2)

$\text{BETAINV}(1 - \alpha, b_v + 1, b - b_v) = \text{BETAINV}(1 - 0.025, 128 + 1, 173 - 128) = 0.80351$

$\text{BETAINV}(\alpha, b_v, b - b_v + 1) = \text{BETAINV}(0.025, 128, 173 - 128 + 1) = 0.66785$

Lower bound of exact 95% CI for vaccine efficacy $= 1 - \frac{0.80351}{2(1 - 0.80351)} = -104.5\%$

Upper bound of exact 95% CI for vaccine efficacy $= 1 - \frac{0.66785}{2(1 - 0.66785)} = -0.5\%$

Calculation of asymptotic confidence interval (shown here for completeness)

$\frac{b_p}{b} = \frac{45}{173} = 0.26012, \frac{b_v}{b} = \frac{128}{173} = 0.73988, \ln\left(1 + \frac{1}{b}\right) = \ln\left(1 + \frac{1}{173}\right) = 0.00576$

Lower bound of asymptotic 95% CI for vaccine efficacy

$$= 1 - exp\left(\ln\left(\frac{1}{2}\left(\frac{128}{45}\right)\right) + 0.00576 + 1.96\sqrt{\frac{1}{173}\left(\frac{(1 - 0.73988)}{0.73988} + \frac{(1 - 0.26012)}{0.26012} + 2\right)}\right) = -100.9\%$$

Upper bound of asymptotic 95% CI for vaccine efficacy

$$= 1 - exp\left(\ln\left(\frac{1}{2}\left(\frac{128}{45}\right)\right) + 0.00576 - 1.96\sqrt{\frac{1}{173}\left(\frac{(1 - 0.73988)}{0.73988} + \frac{(1 - 0.26012)}{0.26012} + 2\right)}\right) = -1.8\%$$

COVID-19 Endpoint

Vaccine efficacy estimate $= 1 - \frac{1}{k}\frac{n_v}{n_p} = 1 - \frac{1}{2}\left(\frac{71}{76}\right) = -53.3\%$

Calculation of exact confidence interval (shown in Figure 2)

$\text{BETAINV}(1 - \alpha, n_v + 1, n - n_v) = \text{BETAINV}(1 - 0.025, 71 + 1, 147 - 71) = 0.56680$

$\text{BETAINV}(\alpha, n_v, n - n_v + 1) = \text{BETAINV}(0.025, 71, 147 - 71 + 1) = 0.39989$

Lower bound of exact 95% CI for vaccine efficacy $= 1 - \frac{0.56680}{2(1 - 0.56680)} = 34.6\%$

Upper bound of exact 95% CI for vaccine efficacy $= 1 - \frac{0.39989}{2(1 - 0.39989)} = 66.7\%$

Calculation of asymptotic confidence interval (shown here for completeness)

$\frac{n_p}{n} = \frac{76}{147} = 0.51701, \frac{n_v}{n} = \frac{71}{147} = 0.48299, \ln\left(1 + \frac{1}{n}\right) = \ln\left(1 + \frac{1}{147}\right) = 0.00678$

Lower bound of asymptotic 95% CI for vaccine efficacy

$$= 1 - exp\left(\ln\left(\frac{1}{2}\left(\frac{71}{76}\right)\right) + 0.00678 + 1.96\sqrt{\frac{1}{147}\left(\frac{(1 - 0.48299)}{0.48299} + \frac{(1 - 0.51701)}{0.51701} + 2\right)} \right) = 35.0\%$$

Upper bound of asymptotic 95% CI for vaccine efficacy

$$= 1 - exp\left(\ln\left(\frac{1}{2}\left(\frac{71}{76}\right)\right) + 0.00678 - 1.96\sqrt{\frac{1}{147}\left(\frac{(1 - 0.48299)}{0.48299} + \frac{(1 - 0.51701)}{0.51701} + 2\right)} \right) = 66.0\%$$

Nonsevere COVID-19 Endpoint

Vaccine efficacy estimate $= 1 - \frac{1}{k}\frac{c_v}{c_p} = 1 - \frac{1}{2}\left(\frac{63}{57}\right) = 44.7\%$

Calculation of exact confidence interval (shown in Figure 2)

$\text{BETAINV}(1 - \alpha, c_v + 1, c - c_v) = \text{BETAINV}(1 - 0.025, 63 + 1, 120 - 63) = 0.61689$

$\text{BETAINV}(\alpha, c_v, c - c_v + 1) = \text{BETAINV}(0.025, 63, 120 - 63 + 1) = 0.43185$

Lower bound of exact 95% CI for vaccine efficacy $= 1 - \frac{0.61689}{2(1 - 0.61689)} = 19.5\%$

Upper bound of exact 95% CI for vaccine efficacy $= 1 - \frac{0.43185}{2(1 - 0.43185)} = 62.0\%$

Calculation of asymptotic confidence interval (shown here for completeness)

$\frac{c_p}{c} = \frac{57}{120} = 0.47500, \frac{c_v}{c} = \frac{63}{120} = 0.52500, \ln\left(1 + \frac{1}{c}\right) = \ln\left(1 + \frac{1}{120}\right) = 0.00830$

Lower bound of asymptotic 95% CI for vaccine efficacy

$$= 1 - exp\left(ln\left(\frac{1}{2}\left(\frac{63}{57}\right)\right) + 0.00830 + 1.96\sqrt{\frac{1}{120}\left(\frac{(1-0.52500)}{0.52500} + \frac{(1-0.47500)}{0.47500} + 2\right)}\right) = 20.3\%$$

Upper bound of asymptotic 95% CI for vaccine efficacy

$$= 1 - exp\left(ln\left(\frac{1}{2}\left(\frac{63}{57}\right)\right) + 0.00830 - 1.96\sqrt{\frac{1}{120}\left(\frac{(1-0.52500)}{0.52500} + \frac{(1-0.47500)}{0.47500} + 2\right)}\right) = 61.1\%$$

Severe COVID-19 Endpoint

Vaccine efficacy estimate $= 1 - \frac{1}{k}\frac{d_v}{d_p} = 1 - \frac{1}{2}\left(\frac{8}{19}\right) = 78.9\%$

Calculation of exact confidence interval (shown in Figure 2)

$BETAINV(1 - \alpha, d_v + 1, d - d_v) = BETAINV(1 - 0.025, 8 + 1, 27 - 8) = 0.50181$

$BETAINV(\alpha, d_v, d - d_v + 1) = BETAINV(0.025, 8, 27 - 8 + 1) = 0.13753$

Lower bound of exact 95% CI for vaccine efficacy $= 1 - \frac{0.50181}{2(1-0.50181)} = 49.6\%$

Upper bound of exact 95% CI for vaccine efficacy $= 1 - \frac{0.13753}{2(1-0.13753)} = 92.0\%$

Calculation of asymptotic confidence interval (shown here for completeness)

$\frac{d_p}{d} = \frac{19}{27} = 0.70370, \frac{d_v}{d} = \frac{8}{27} = 0.29630, ln\left(1 + \frac{1}{d}\right) = ln\left(1 + \frac{1}{27}\right) = 0.03637$

Lower bound of asymptotic 95% CI for vaccine efficacy

$$= 1 - exp\left(ln\left(\frac{1}{2}\left(\frac{8}{19}\right)\right) + 0.03637 + 1.96\sqrt{\frac{1}{27}\left(\frac{(1-0.29630)}{0.29630} + \frac{(1-0.70370)}{0.70370} + 2\right)}\right) = 50.1\%$$

Upper bound of asymptotic 95% CI for vaccine efficacy

$$= 1 - exp\left(ln\left(\frac{1}{2}\left(\frac{8}{19}\right)\right) + 0.03637 - 1.96\sqrt{\frac{1}{27}\left(\frac{(1-0.29630)}{0.29630} + \frac{(1-0.70370)}{0.70370} + 2\right)}\right) = 90.4\%$$

Burden of Disease (BOD) Endpoint

$$\bar{y}_p = 1 + \frac{d_p}{n_p} = 1 + \frac{19}{76} = 1.25000$$

$$\bar{y}_v = 1 + \frac{d_v}{n_v} = 1 + \frac{8}{71} = 1.11268$$

$$s_p^2 = \frac{d_p(n_p - d_p)}{n_p^2} = \frac{19(76 - 19)}{76^2} = 0.18750$$

$$s_v^2 = \frac{d_v(n_v - d_v)}{n_v^2} = \frac{8(71 - 8)}{71^2} = 0.09998$$

$$\hat{\pi}_p = \frac{n_p}{n} = \frac{76}{147} = 0.51701$$

$$\hat{\pi}_v = \frac{n_v}{n} = \frac{71}{147} = 0.48299$$

$$ln\left(1 + \frac{1}{n}\right) = ln\left(1 + \frac{1}{147}\right) = 0.00678$$

$$\widehat{RR}_{BOD} = \frac{1}{k}\frac{n_v}{n_p}\frac{\bar{y}_v}{\bar{y}_p} = \frac{1}{2}\left(\frac{71}{76}\right)\left(\frac{1.11268}{1.25000}\right) = 0.41579$$

Vaccine efficacy estimate $= 1 - \widehat{RR}_{BOD} = 1 - 0.41579 = 58.4\%$

Calculation of asymptotic confidence interval (shown in Figure 2)

$$\frac{\hat{\pi}_v[s_v^2 + (1 - \hat{\pi}_v)\bar{y}_v^2]}{(\hat{\pi}_v\bar{y}_v)^2} = \frac{0.48299[0.09998 + (1 - 0.48299)(1.11268^2)]}{[(0.48299)(1.11268)]^2} = 1.23762$$

$$\frac{\hat{\pi}_p[s_p^2 + (1 - \hat{\pi}_p)\bar{y}_p^2]}{(\hat{\pi}_p\bar{y}_p)^2} = \frac{0.51701[0.18750 + (1 - 0.51701)(1.25000^2)]}{[(0.51701)(1.25000)]^2} = 1.16632$$

Lower bound of asymptotic 95% CI for vaccine efficacy

$$= 1 - exp\left(ln(0.41579) + 0.00678 + 1.96\sqrt{\frac{1}{147}(1.23762 + 1.16632 + 2)}\right) = 41.2\%$$

Upper bound of asymptotic 95% CI for vaccine efficacy

$$= 1 - exp\left(ln(0.41579) + 0.00678 - 1.96\sqrt{\frac{1}{147}(1.23762 + 1.16632 + 2)}\right) = 70.2\%$$

COVID-19 and BOD as Dual Primary Endpoints

As noted on page 6 of this Appendix, if COVID and BOD were dual primary endpoints, to calculate the multiplicity-adjusted 95% confidence intervals for each of these two endpoints, the 2.5[th] percentile of the standard normal distribution (resulting in the $Z_{1-\alpha} = 1.96$ term in the unadjusted confidence interval calculation) would be replaced with the 2.5[th] percentile of the distribution of Z_* (with $\hat{\rho}$ replacing ρ).

In this hypothetical data example:

$$\hat{\rho} = \frac{\sqrt{\frac{1}{147}\left(\frac{(1-0.48299)}{0.48299} + \frac{(1-0.51701)}{0.51701} + 2\right)}}{\sqrt{\frac{1}{147}(1.23762 + 1.16632 + 2)}} = 0.95372$$

The distribution of Z_* (with $\hat{\rho}$ replacing ρ) is:

$f(z_*) = 2\phi(z_*)\Phi\left(-\frac{1-0.95372}{\sqrt{1-0.95372^2}}z_*\right)$ and the 2.5[th] percentile of this distribution is -2.069 obtained using 1 million simulations.